REMARKS

Claims 11, 12, and 14-31 are pending in the instant application.

Claims 23 has been amended to recite that W is polyethylene glycol (PEG) or a cyclodextrin comprising polythelene glycol (PEG). Support for this amendment can be found in the specification and claims as originally filed, including, but not limited to Paragraphs [0050] to [0047] of the corresponding U.S. Publication No. 2005/0249740. No new matter has been added.

Applicants respectfully reserve the right to pursue any non-elected, canceled or otherwise unclaimed subject matter in one or more continuation, continuation-in-part, or divisional applications.

Reconsideration and withdrawal of the objections to and the rejections of this application in view of the amendments and remarks herewith, are respectfully requested, as the application is believed to be in condition for allowance.

Statement of Substance of Interview

On November 5, 2009, Applicants' undersigned representative participated in a telephonic interview with Examiner Gudibande, during which a proposed amendment to Claim 23 was discussed. The Examiner noted the similarity to the Examiner's prior proposed Examiners amendment (See Interview Summary Paper No. 20090829 which states no separate record is required). The Examiner stated that the amendment could be submitted After Final for consideration. No final agreement as to the allowability of the claims was reached.

Rejections under 35 U.S.C. §102(e)

Claims 23 and 29 remain rejected under 35 USC § 102 (e) as allegedly anticipated by United States Patent Publication No 2002/0169125 to Leung ("Leung"). The Examiner alleges that Leung discloses a polyanionic polymer conjugated to a drug selected from the group tubulysin or dolastatin which exhibits cytotoxic properties and that the drug can be conjugated to the polyanionic polymer through an indirect linkage such as a bifunctional spacer.

As previously stated, claims 23 and 29 are directed to specific derivatives which are linked to a polymer comprising a polyethylene glycol (PEG) with a specified point of attachment.

Leung is directed to recombinantly-produced polyanionic polymers, i.e. to bin-molecules as described in the instant priority application (DE 102 30 075.6). Leung only mentions tubulysins among a long list of possible drugs and does not disclose any example for a tubulysin linked to such a polyanionic polymer. As such, Applicants respectfully submit that nothing in Leung anticipates the claimed invention.

Nevertheless, as amended, the compounds of the claimed invention are directed to compounds having the formula U-V-W wherein W is a polyethylene glycol (PEG) or a cyclodextrin comprising polyethylene glycol (PEG).

Again, Leung is related to the use of recombinantly-produced polyanionic polymers. Nothing in Leung teaches or suggests the linkage of tubulysin to polyethylene glycol (PEG) or a cyclodextrin comprising polyethylene glycol (PEG) though a linker. Indeed, the Examiner admits that Leung does not teach polyethylene glycol as the polymer on Page 5 of the office action.

As such, Leung cannot anticipate the claimed invention. Applicant respectfully requests that the rejections of the claims under 35 U.S.C. § 102(e) be withdrawn.

Rejections under 35 U.S.C. §103(a)

Claims 12 and 14-31 remain rejected under 35 USC § 103 (a) as allegedly unpatentable over United States Patent Publication No 2002/0169125 to Leung ("Leung") in view of Greenwald *Journal of Controlled Release* 74, 159-171 ("Greenwald") and Duncan, 2001 *Journal of Controlled Release* 74, 135-146 ("Duncan").

The Examiner again alleges that Leung discloses a polyanionic polymer conjugated to a drug selected from the group tubulysin or dolastatin which exhibits cytotoxic properties and that the drug can be conjugated to the polyanionic polymer through an indirect linkage such as a bifunctional spacer.

As discussed above Leung is directed to recombinantly-produced polyanionic polymers, i.e. to bin-molecules as described in the instant priority application (DE 102 30 075.6). Leung only mentions tubulysins among a long list of possible drugs and does not disclose any example

for a tubulysin linked to such a polyanionic polymer. Nothing in Leung teaches or suggests the linkage of tubulysin to polyethylene glycol (PEG) or a cyclodextrin comprising polyethylene glycol (PEG) though a linker. Finally, Leung only discloses the use of a polyanionic polymer to increase the water solubility and/or the half-life of the drug.

Greenwald does nothing to rectify the deficiencies of Leung. As discussed in Applicants' prior responses and in the Rule 132 Declarations of record, it is shown that by coupling tubulysin A with a PEG ester, amide or phenol, the activity of the respective compounds in two cancer cell lines can be dramatically reduced, thus, leading to tubulysin derivatives with lower toxicity.

Greenwald classifies PEG-drugs as permanently bonded PEG-drugs (cf. chapter 2, page 160) and as non-permanently bonded PEG-drugs, i.e. PEG prodrugs (chapter 3, page 160).

According to Greenwald, permanently bonded PEG-drugs comprise PEG linkers of molecular weight 2000 to 5000, i.e. low molecular weight PEG. As can be taken from the Declaration filed November 30, 2006, tubulysin A PEG-derivatives having a PEG linker with high molecular weight, such as 35kDa or 40kDa provide better results with regard to the object of the present invention than low molecular weight PEGs. This finding is by no means rendered obvious by Greenwald suggesting to use permanently bonded PEG-drugs wherein the PEG linker has a molecular weight of from 2000 to 5000.

On the contrary, Greenwald ***teaches away*** from the instant invention, further rebutting any case of *prima facie* obviousness contended.

As mentioned above, chapter 3 of the Greenwald publication discloses PEG prodrugs. Greenwald states that a prodrug is a biologically inactive derivative of a parent drug molecule that usually requires an enzymatic transformation within the body in order to release the active drug, and has improved delivery properties over the parent molecule (cf. page 160, right-hand column, last paragraph). In other words, a prodrug is formed in order to render a parent drug molecule in a condition to enable absorption of the drug molecule in the human body. Once the prodrug has entered the human body, it is enzymatically transformed to release the active drug.

However, this scenario does not apply to the tubulysin derivatives according to the present invention. As stated in paragraph [0003] of the present specification, tubulysins possess an extremely high cytotoxicity. If the tubulysin derivatives released free tubulysins immediately

after absorption in the human body, the free tubulysins would immediately exert their cytotoxic effects resulting in extensive cell death of normal cells. As a consequence, such tubulysin prodrugs are not selective and are connected with serious side effects. As stated in paragraph [0004] of the present specification, the object of the present invention is to enhance selectivity of tubulysins.

Applicant has surprisingly found that tubulysin derivatives according to claim 23 are stable in plasma/buffer and, thus, less cytotoxic than natural tubulysins as indicated above with regard to the experimental data set forth in the Rule 132 Declarations of record. Furthermore, Applicant has surprisingly found that once the tubulysin derivatives have entered a cancer cell, free tubulysin is released and can exert its high cytotoxic activity directly in the cancer cell. Accordingly, the compounds according to the present invention provide for drug targeting of tubulysin selectively to cancer cells. These findings are by no means rendered obvious by the publications of Leung in combination with Greenwald.

In Applicants' last response, Applicant submitted a copy of Schluep et al. *Clin, Cancer Res*, 2009 15(1) 181-189, which discloses further experimental data of a tubulysin derivative which is linked to a polymer comprising PEG. The Examiner has taken the citation of the Schluep reference as acknowledging that the conjugation of toxic drugs to PEG improve the activity and lower the toxicity of a drug is well known in the art. Applicant respectfully disagrees. Indeed, the Applicant submitted the Schluep article, which is dated nearly six years after the filing of the instant application to add further support to the data which was shown by Applicant (and evidenced in the Rule 132 Declarations of record) but not recognized by Leung or any of the prior art. The Schluep article, at best, highlights what is well known in the art as of 2009, which is due in no small part to Applicant's own invention.

Indeed, As previously argued, the Schluep article and the poster attached to the previously submitted Declaration, demonstrate that tubulysin derivatives additionally comprising a cyclodextrin group provide added benefits. In fact, cyclodextrin-PEG-polymer conjugates of tubulysin show high antiproliferative activity in human cancer cells (cf, table 1), but are significantly less toxic than tubulysin A (cf. table 2). As evident from table 3 and graph 1, cyclodextrin conjugates of tubulysin are better tolerated than vinblastine and tubulysin A and lead to a significant increase in tumor growth delay, inhibit the formation of new tumor cells and at the same time reduce the number of existing tumor cells.

Finally, as previously argued, Duncan does nothing to rectify the deficiencies of Leung nor Greenwald. Like Greenwald, Duncan does not disclose conjugates comprising a tubulysin derivative and a polymer comprising a PEG. Therefore, like Greenwald, Duncan cannot render the present invention obvious. In particular, Duncan does not disclose or suggest the conjugation of the specific tubulysin derivatives of formula (I) with a polymer comprising PEG via a linker at residue R^{19} or R^{20}.

In sum, neither Leung, Greenwald nor Duncan teach or suggest a tubyulysin derivative bound to a PEG or a cyclodextrin comprising a PEG. Neither Leung nor Duncan teach or suggest the inclusion of a PEG and Greenwald teaches away from the use of PEG as the immediate reversability of the PEG-prodrugs described in Greenwald would not reduce the toxicity of the drugs involved. As such, one of ordinary skill in the art at the time of the invention would have had no motivation to combine Leung, Greenwald and Duncan to arrive at the instantly claimed compounds and methods and would further have had no expectation of success in achieving a drug-PEG conjugate with the surprising stability in plasma/buffer and lower cytotoxicity of the instant conjugates.

As such, Applicants respectfully request that the rejections of the claims under 35 U.S.C. § 103(a) be withdrawn.

Double Patenting Rejection

Claim 23 remains provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 19-32 of copending Application No. 10/520,793 in view of Leung.

Without conceding the validity of the Examiner's contention, Applicant submits herewith a duly executed Terminal Disclaimer in compliance with 37 C.F.R. §1.321(c) over co-pending Application Nos. 10/520,793. Accordingly, Applicant respectfully requests withdrawal of the provisional obviousness-type double patenting rejection.

CONCLUSION

In view of the foregoing, reconsideration and withdrawal of all rejections, and allowance of the instantly claimed invention are earnestly solicited. If a telephone conversation with Applicant's attorney would help expedite the prosecution of the above-

identified application, the Examiner is urged to call Applicant's attorney at the telephone number below.

Applicant believes that there are no additional fees due with this response. However, if a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. 04-1105 for any fee(s) due with this response.

Dated: December 15, 2009

Respectfully submitted,

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